EBV tests which are available for diagnosis of occasional patients with puzzling manifestations. Actually, CMV mononucleosis and toxoplasmosis are usually readily differentiated from heterophil positive IM by appropriate clinical, microbial and immunologic observations.

The genesis of heterophil antibody, a hallmark of IM, remains one of the interesting unresolved puzzles in this common disease. Heterophil antibodies were first described by Forssman[2] in 1911. Paul and Bunnell[3] subsequently noted their presence in four persons with IM, a disease which had been clearly differentiated from its British cousin, glandular fever, by Sprunt and Evans in 1920.[4] Davidsohn and Walker's[5] landmark discovery that the heterophil antibody of IM differed from the Forssman antibody of serum sickness provided the cornerstone of clinical laboratory diagnosis of IM. That the hetrophil antigen itself is not the cause of IM was shown by Leikola and Aho, who observed typical heterophil antibody responses in the absence of infectious mononucleosis (IM) in a group of volunteers immunized with cells containing the heterophil antigen.[6] Even though heterophil antibody may be an epiphenomenon in IM, its presence is a highly specific and sensitive finding. Fiala and co-workers have correctly pointed out the very low incidence of false negative and positive results for this test.

Clearly, the most exciting recent discovery in the disease is its relationship to the Epstein-Barr virus. Paradoxically, this probable viral cause of IM has provoked new questions regarding EBV's role as a human tumor virus. The discovery that EBV was causally related to IM was made serendipitously in 1967 by the Henles,[7] who were able to establish a continuous lymphoid cell line from the blood of a person only after she contacted IM. Since then virtually all long-term human lymphoblastoid cell lines have been shown to be infected with EBV. Furthermore, the considerable body of seroepidemiologic and virologic evidence compiled in the last ten years leaves little doubt that IM is the result of EBV infection.[8]

Perhaps the most intriguing mystery of EBV's relationship to IM is why the disease is, in fact, self-limiting. Under different circumstances, EBV infections have been causally linked to nasopharyngeal carcinoma and Burkitt lymphoma. A number of possible explanations of this spectrum of responses to EBV infection comes to mind. First, genetic differences in the immune response to many antigens are now recognized and the association of transplantation antigens and disease is well documented. However, no clear-cut genetic predisposition correlating EBV with its associated diseases has been shown to exist. Second, EBV infects B-lymphocytes and in IM there is an intense concomitant proliferation of T-cells presumably in response to the infected B-lymphocytes. Failure of the T-cell population to effectively control the infection might lead to unrestricted B-cell proliferation and eventually a tumor. Finally, socioeconomic, geographical and many other environmental factors are intimately involved in the outcome of EBV infections, especially in view of the high correlation of African Burkitt lymphoma, EBV and endemic malaria. In my opinion, the definitive proof of the existence of human tumor virus may emerge from unraveling the mystery of the subtle host-virus interplay responsible for limited lymphoproliferation in IM.

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Management of Patients with Aortic Valve Disease

FOR PROPER MANAGEMENT of patients with aortic valve disease, physicians should have knowledge of current information concerning the structural and functional changes that occur in the heart as a consequence of the pressure and volume overload states from aortic valve disease, the relationship of these changes to clinical findings and to prognosis, and the effects of surgical therapy for aortic valve disease. For a number of years, there have been methods available for evaluating the severity of the mechanical defects of aortic valve stenosis and insufficiency.[1,2] More

recently, methods have become available for evaluating the extent of left ventricular hypertrophy, dilatation and myocardial performance in the presence of aortic valve disease.[3] From studies in experimental animals and in man, it is clear that the left ventricular response to a chronic pressure overload, as occurs in aortic valve stenosis, is ventricular hypertrophy with an increase of wall thickness, while chamber volume remains essentially normal. The increase of diastolic pressure which is often observed in patients with aortic stenosis appears related to the increased wall thickness rather than to altered stiffness of the myocardium per se.[4] These conclusions are based on studies of ventricular wall stress during diastole or of the normalized force within the wall which is acting to increase wall dimensions with ventricular diastolic filling. The response to a chronic ventricular volume overload, as occurs with aortic valve insufficiency, is both ventricular dilatation and hypertrophy with a modest increase of wall thickness. It is of interest that ventricular hypertrophy is usually more pronounced in aortic valve insufficiency than in aortic stenosis.[5] On the basis of more recent studies, systolic performance of the hypertrophied ventricle appears to be normal, at least in the early compensated phases of adjustment to the chronic pressure and volume overload states.[6] However, the long-term effect of the mechanical overload from chronic aortic valve disease, as seen in man, is a depression of myocardial performance. The biochemical and ultrastructural changes that account for this reduced performance are not currently understood. The depressed performance is associated with further dilatation, hypertrophy and often myocardial fibrosis, and is accompanied by a reduced systolic ejection fraction and a reduced normalized velocity of circumference of fiber change, or Vcf. Recent studies show that patients with depressed ventricular performance, as evidenced by cardiomegaly, left ventricular dilatation and a low ejection fraction, have a reduced prognosis for survival, with or without surgical replacement of the aortic valve.[7,8]

In managing a patient with aortic valve disease, it seems important to recommend surgical intervention before the development of depressed myocardial function. There is evidence that following aortic valve replacement there is, in many patients, regression of both ventricular dilatation and hypertrophy, although values may not completely regress to normal.[9,10] Other studies indicate that this regression of ventricular dilatation and hypertrophy does not occur, or is minimal, in patients with aortic valve insufficiency that is associated with depressed myocardial performance.[11] Methods for clinical evaluation and for determining when heart catheterization and surgical operation should be recommended are described in some detail in the informative symposium, "The Medical and Surgical Management of Patients with Aortic Valve Disease" which is published in this issue. The diagnostic studies are directed toward evaluation of the mechanical severity of the aortic valve disease, myocardial performance and complicating lesions of other valves, and for the detection of significant coronary artery disease. Aortic valve surgical therapy may be indicated on the basis of the severity of the aortic stenosis or insufficiency, or because of the development of depressed myocardial function combined with a significant mechanical defect from the aortic valve disease. In other patients, operation may not be indicated because the mechanical defect is trivial and depressed myocardial function is severe; however, the minimal severities of aortic stenosis or insufficiency and levels of depressed ventricular performance for such decisions have not been precisely defined.

I have some minor disagreements and additional suggestions for evaluation of patients from those given in the symposium. I have not found that the left ventricular ejection time (LVET) is particularly helpful in evaluating the severity of aortic stenosis and I question whether this determination is worth the time and expense. The LVET is difficult to measure in aortic stenosis and there are too many factors other than the severity of the aortic stenosis that may alter the LVET. In addition, the LVET is not helpful in evaluating the severity of aortic stenosis in the presence of mixed stenosis and insufficiency, which is so often present. If there is a problem in evaluating the location and significance of heart murmurs, we have found that the new noninvasive technique of Doppler echocardiography is often helpful in addition to standard M-mode echocardiography.[12] If there are questions regarding the severity of aortic stenosis, whether heart catheterization is indicated or to what extent physical activity should be limited, a carefully carried out maximal treadmill stress test with frequent monitoring of arterial blood pressure can be helpful. Exertional hypotension is a frequent early finding in patients with hemodynamically significant aortic stenosis.

The spectacular advances in cardiac surgical operation for aortic valve replacement and in the outlook and prognosis of patients with aortic valve replacement are reviewed by Dr. Daily in the symposium referred to above. For patients with aortic valve disease to derive the maximum benefit from these advances, appropriate evaluation and recommendation for operation are important. With the current low risk of operation for elective valve replacement, improved surgical techniques to minimize myocardial damage at the time of open heart surgical procedures and the improved function, durability and risk of complications of prosthetic and tissue valves, a more aggressive approach to earlier operation in a patient with hemodynamically significant aortic valve insufficiency might well be justified.

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